understanding the nature of the MAIT cell TCR–MR1 interaction and the subsequent development of broad-spectrum MAIT cell–dependent vaccines. The studies by Le Bourhis *et al.*[2] and Gold *et al.*[5] represent a large step in understanding MAIT cell biology. Now we just need to know exactly what our MAITs are seeing and whether we can depend on them in a crisis.

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MafB as a type I interferon rheostat

Hozumi Motohashi & Kazuhiko Igarashi

Type I interferons are produced by almost all nucleated cells in response to virus infection. MafB is now shown to modulate the efficiency of interferon production by setting a threshold for IRF3-dependent transcription.

Type I interferons, including interferon-α (IFN-α) and IFN-β, have been described as a double-edged sword because they have a protective role in antiviral responses but have a pathological role in autoinflammatory disease. Suppression of type I interferon signaling in pancreatic beta cells causes vulnerability to viral infection and rapid death of the beta cells, which indicates that an increase in these cytokines in the acute phase of infection contributes to host cell defense[1]. In contrast, a chronic increase in systemic or local concentrations of type I interferon has adverse effects, mainly through the induction of self-reactive cytotoxic T cells[2]. Thus, deciphering how type I interferon production is regulated is key to understanding the pathogenesis of virus-induced autoimmune diseases. Using a transcriptional reporter screen with an *IFNB1* enhancer-promoter and cDNA expression library, Kim and Seed have identified MafB, one of the large Maf transcription factors, as a negative regulator of the expression of type I interferon genes[3]. Their results suggest that negative regulation is critical to avoiding runaway amplification of the interferon response and provide insights into the etiology of autoinflammatory disease.

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Maf proteins are basic-region leucine zipper–type transcription factors, and they bind as dimers to a specific DNA element called the 'Maf-recognition element' (MARE). Large Maf homodimers activate transcription, whereas small Maf heterodimers activate or repress transcription depending on the dimer partner molecule, for example, CNC or Bach. MARE-dependent regulation is generally regarded as the basis of the *in vivo* function of Maf-containing dimers. The structural basis of this unique DNA recognition by Maf proteins has been clarified through X-ray crystallography, which has provided a good explanation for the connection between the target-gene selectivity of Maf dimers and their biological functions[4]. The various Maf-containing dimers regulate diverse biological events, including pancreatic islet alpha- and beta-cell development, expression of glucagon and insulin genes, monocyte-macrophage development, T cell development, class-switch recombination, platelet production and oxidative stress response. The glucagon and insulin genes in developing pancreatic alpha and beta cells and the crystallin gene in lens epithelial cells are typical MafB targets regulated through MARE (**Fig. 1a**). The present study by Kim and Seed now extends MafB function to *IFNB1* regulation that is independent of MARE[3].

Regulation of the gene encoding IFN-β is one of the most thoroughly analyzed transcriptional systems and provides the prototypical example of an enhanceosome[5]. The promoter region of this gene has four consecutive *cis*-regulatory elements, to which the transcription factors AP-1, IRF3 and NF-κB bind in a highly cooperative way to achieve fully active transcription. This enhancer complex forms the enhanceosome, alters the local chromatin architecture and recruits the coactivator CBP and RNA polymerase II machinery to the promoter. Under normal conditions, cells do not express the gene encoding IFN-β, but viral infection activates AP-1, IRF3 and NFκB through post-translational mechanisms and makes them assemble onto the gene's promoter. Kim and Seed have identified MafB as a disruptor of the enhanceosome by showing that MafB associates with IRF3 and displaces CBP[3] (**Fig. 1b**). Notably, as promoter regions of other IRF3-dependent genes, such as those encoding the chemokines CCL5 (RANTES) and CXCL10 (IP10) and the ubiquitin-like modifier ISG15, also have binding sites for many transcription factors, including AP-1 and NF-κB[6], a similar enhanceosome probably operates the transcriptional regulation of these genes in response to viral infection. The paper by Kim and Seed shows that MafB does indeed inhibit the promoter activity of the gene encoding RANTES[3], which suggests a wider contribution of MafB in the tuning of antiviral responses.

Intriguingly, Kim and Seed show that Mafb expression is repressed after stimulation by IFN-β inducers[3]. MafB abundance is inversely correlated with that of IFN-β, which suggests that MafB sets the threshold for transcription mediated by IRF3 during antiviral responses. This suggests the following scheme: under normal conditions, MafB has high expression and is poised to inhibit IRF3-mediated transcription triggered by adventitious activation of the antiviral response (**Fig. 1b**, top). This is advantageous, as uncontrolled firing of *IFNB1* genes is thought to result in a predisposition to autoinflammatory diseases. During the acute phase of viral infection, MafB expression decreases, which allows activation of *IFNB1* and subsequent antiviral activity (**Fig. 1b**, middle). If high MafB

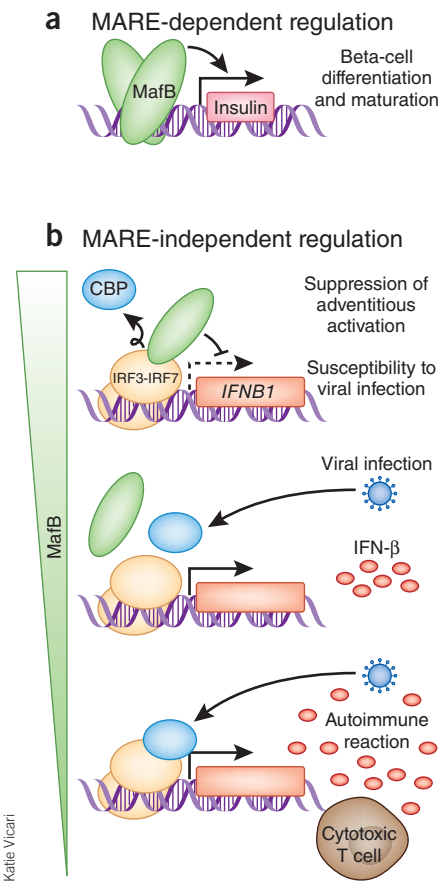

Figure 1 The dual modes of MafB function. (**a**) MARE-dependent transcription. The MafB homodimer binds to MARE DNA sequences and activates transcription. MafB promotes the differentiation and maturation of islet beta cells and activates the insulin gene through MARE. (**b**) MARE-independent transcription. After adventitious activation of antiviral responses under normal conditions in which MafB expression is high, MafB associates with IRF3, displaces CBP and inhibits transcription of *IFNB1* (top). After viral infection, *MAFB* expression decreases and the inhibitory effect on *IFNB1* is relieved (middle). In the absence of MafB, hyperactivation of *IFNB1* is triggered by viral infection (bottom). Excessive MafB in the acute phase of infection represses the production of IFN-β, possibly causing the susceptibility to viral infection (top). Insufficient MafB during the chronic phase of infection augments IFN-β production, triggering an autoinflammatory response (bottom).

expression is sustained, *IFNB1* expression is insufficient, which results in vulnerability to viral infection (**Fig. 1b**, top). When lower expression of MafB is prolonged, hyperactivation of *IFNB1* probably induces the development of autoreactive immune cells (**Fig. 1b**, bottom). Using kinetic modeling, Kim and Seed assess the contribution of MafB to the system at various concentrations and find that the simulation supports the proposal of a strong dependency of IFN-β expression on MafB concentration[3]. Unfortunately, several critical parameters and predictions of the modeling have not been examined experimentally in this study. An obvious but critical question, then, is whether the ultimate IFN-β response varies depending on the initial concentration of MafB in cells.

An important implication of the work by Kim and Seed relates to the pathogenesis of type I diabetes. This common autoimmune disease results from selective and progressive destruction of islet beta cells. The etiology of autoimmune diseases often involves both genetic and environmental factors, and viral infection has been suggested to be one such environmental trigger of the autoimmune reaction. Linkage between the progression of type I diabetes and enterovirus infection, especially coxsackievirus infection, has emerged from intensive epidemiological and clinical work[7]. Kim and Seed demonstrate that MafB suppresses *Ifnb1* promoter activity and allows more efficient replication of virus in a mouse pancreatic beta-cell line[3]. They also show that MafB expression in human pancreatic islets, especially in beta cells, is relatively high. Thus, larger amounts of MafB in beta cells might be an important susceptibility factor for type I diabetes. Notably, myeloid commitment is facilitated in *Mafb*-heterozygous mice[8], which therefore warrants consideration of the effect of haploinsufficiency in understanding MafB function. Thus, the basal and induced *Ifnb1* expression in *Mafb*-heterozygous and *Mafb*-homozygous cells examined in the present study will need to be reevaluated through the exploitation of wild-type cells.

Another remarkable finding by Kim and Seed is the unique molecular mechanism of MafB function[3]. Their work shows that the DNA-binding activity of MafB is not required for the inhibitory effect upon IRF3. Indeed, very few examples of a MARE-independent function for Maf and CNC proteins have been reported. Large Maf proteins, including MafB, enter the transcription complex via other DNA-binding proteins, including Ets-1, c-Myb and Pax6, and modulate the function of the complex[9], whereas Bach1, the heterodimeric partner of small Maf proteins, forms a corepressor complex for the tumor suppressor p53 and inhibits p53-mediated cell senescence[10]. The MARE-independent activities of the Maf family and its partners seem to contribute to the generation of diversity and complexity in transcriptional regulation. More cases of MARE-independent regulation will probably emerge in the future and identify previously unknown crosstalk between Maf and other transcription factors.

The work presented by Kim and Seed is a nice kick-off for the study of MafB function in autoimmune disease. There are several important future questions to consider. First, more conclusive evidence for the contribution of MafB as a rheostat for *IFNB1* regulation and development of autoimmune disease will need to be tested *in vivo*. As Kim and Seed have shown that all large Maf proteins antagonize the effect of type I interferon inducers on *IFNB1* reporter activity[3], *in vivo* results obtained from mouse experiments need to be considered in the context of a potential functional redundancy between MafB and other large Maf proteins. Indeed, pancreatic islets of adult mice express many large Maf proteins, such as MafA, MafB and c-Maf[11]. Likewise, overlapping expression of large Maf proteins might be observed in human tissues if their expression profiles are described more precisely. Second, association studies of the manifestation of type I diabetes and polymorphisms in the *MAFB* locus will need to be made in humans. Indeed, *BACH2*, which encodes a partner of the small Maf protein, has been reported as a candidate susceptibility gene for human type I diabetes[12], which may indicate some functional association between Bach2 and MafB. Third, the structure of MafB in association with IRF3 will need to be characterized in more detail to allow the rational design of small molecules targeting MafB. If it is assumed that higher expression of MafB in beta cells is the main cause of vulnerability to enterovirus infection, as suggested by Kim and Seed, directed therapeutic inhibition of MafB might be a good strategy for the prevention of type I diabetes. Conversely, MafB activation will be desirable in cases of chronic activation of *IFNB1* for the amelioration of autoinflammatory responses. Addressing these issues should open a door to new molecular strategies aimed at the prevention and treatment of autoinflammatory diseases.

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